REMARKS

I. Amendment To The Title and Claims

The Title of the invention has been amended to describe the subject matter of the invention.

Claims 1, 2, 9 and 23 have been amended and claims 6-8, 10-22 and 24-26 have been canceled without prejudice. Claims 27-34 have been added. Upon entry of the present amendments, claims 1-5, 9, 23 and 27-34 are pending in this application. No new matter has been introduced by the amendments, and their entry is respectfully requested.

Claims 1 and 23 have been amended to delete "preventing, modifying or managing" and to recite "complex regional pain syndrome" in place of "pain." Support for this amendment may be found, for example, in original claims 8 and 9 and on page 4, line 26 to page 6, line 28 of the specification.

Claims 1 and 23 have also been amended to delete "a therapeutically or prophylactically effective amount of an immunomodulatory compound" and recite "about 5 to about 50 mg per day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione." Support for this amendment may be found, for example, on page 18, line 24 and in the chemical structure shown at the top of page 19 of the specification.

Claim 2 has been amended to delete "or prophylactically."

Claim 9 has been amended to depend from claim 1.

New claim 27 is supported by, for example, claim 15 and the specification at page 18, line 24.

New claims 28-30 are supported by, for example, original claim 1, and the specification at page 8, lines 33-34, page 11, lines 3-5 and page 13, lines 1-22.

New claims 31 and 32 are supported by, for example, the specification at page 13, lines 1-22.

New claim 33 is supported by, for example, the specification at page 35, line 25 to page 39, line 24.

New claim 34 is supported by, for example, the specification at page 35, lines 26-31 and page 36 lines 7-18.

By the amendments, Applicant does not acquiesce to the propriety of any of the Examiner's rejections and does not disclaim any subject matter to which Applicant is entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997). Further, Applicant reserves the right to prosecute the subject matter of any canceled or withdrawn claims in one or more continuation, continuation-in-part, or divisional applications.

II. Claims Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-6, 8-9, 15-16 and 23 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to provide an enabling disclosure. Specifically, the Examiner alleges that the specification does not enable "a method of preventing or modifying pain, or administering a prophylactically effective amount of a second agent." (Office Action, page 4). The Examiner, however, admitted that the specification is enabling for a method of treating neuropathic pain. (Id.).

Solely to promote the allowance of the case and without acquiescing to the Examiner's rejection, the claims have been amended to delete "a method of preventing or modifying pain, or administering a prophylactically effective amount of a second agent." Claims 6, 8 and 15-16 have been canceled and the rejection for these claims is moot. As the Examiner himself admitted that the specification is enabling for a method of treating neuropathic pain, amended claims 1, 9 and 23 are enabled. In view of the amendments and the following discussions, Applicant respectfully submits that the rejection is moot and must be withdrawn.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. Manual of Patent Examining Procedure (hereafter "MPEP") § 2164.04, (citing *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993)). Furthermore, "[a] specification disclosure...must be taken as being in compliance with the enablement requirement...unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *Id.* (emphasis added).

The amended claims recite, *inter alia*, methods of treating complex regional pain syndrome by administering to a patient about 5-50 mg per day of a specific compound, 3-

(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. The specification clearly discloses that the recited disease can be treated with the recited compound. *See*, for example, page 4, line 26 to page 6, line 28; page 18, last paragraph to page 19, first paragraph; and page 22, line 26 to page 26, line 20. It is also disclosed that the recited compound can be prepared by synthetic procedures, as described in the specification, *e.g.*, page 19. Dosages and routes of administration of the compound are disclosed, for example, on page 22, line 26 to page 26, line 20, and pages 32-40 of the specification.

Therefore, all that is required for those of ordinary skill in the art to practice the claimed invention is to administer the specified amount of the recited compound using the specified routes of administration to the specified patient population. In view of the foregoing, the specification provides a sufficient guidance as to treating complex regional pain syndrome. Thus, one skilled in the art would have been able to make or use the claimed invention without undue experimentation.

Further, Applicant notes that the specification includes working examples for animal pain models and clinical studies in patients with complex regional pain syndrome. *See*, Examples 5.3 to 5.4 on pages 43-47. Thus, the specification demonstrates that the recited compound is pharmacologically active to treat the disease and the present claims are enabled.

Next, claims 2-5 recite methods of treating complex regional pain syndrome by administration of the compound of claim 1 with a second active agent. The specification discloses examples of conventional therapeutics that can be used as second active agents to treat pain (*See*, *e.g.*, page 27, lines 7-24). The specification further discloses methods of combination therapy with a second active agent. (*See*, *e.g.*, page 26, line 21 to page 31 line 6). Thus, the specification provides sufficient information and guidance to those of ordinary skill in the art to make and use the claimed invention.

Applicant respectfully submits that use of a second active agent for use with the compounds recited in the instant claims would require only routine experimentation. Merely routine experimentation is not undue. *See In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir 1988). The determination by a physician as to whether any agent is effective in treating a disease in a given patient is a routine practice and is always performed for every pharmaceutical. The specification provides a detailed description of methods using the second active agent in the combination therapy. (*See*, *e.g.*, page 26, line 21 to page 31, line 6). The specification teaches which agents to use, and how much of the agents are used. (*See*, *e.g.*, page 27, lines 3-24). One of ordinary skill in the art, armed with the

information presented in the specification, has adequate guidance to practice the claimed invention. Applicant respectfully submits that one reasonably skilled in the art could make or use the invention as claimed without undue experimentation.

In sum, Applicants respectfully submit that: (1) the specification provides sufficient information and guidance to those of ordinary skill in the art to make and use the claimed invention; (2) the Examiner did not provide any factual or legal basis to doubt that the claims are enabled; and (3) to the extent any experimentation is necessary, such experimentation is not undue. Therefore, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

III. Claims Rejections under 35 U.S.C. § 102

A. Claims 1, 6, 8 and 9 are not anticipated by Rajkumar, *et al.*

Claims 1, 6, 8 and 9 stand rejected under 35 U.S.C. § 102(b) as being unpatentable over Rajkumar, *et al.* The Examiner alleges that claims 1, 6, 8 and 9 are anticipated because Rajkumar teaches the use of thalidomide to treat complex regional pain syndrome (Office Action, page 14). Applicant respectfully disagrees.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP § 2131 (*citing Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Rajkumar allegedly reports the use of thalidomide to treat reflex sympathetic dystrophy, also known as complex regional pain syndrome in a single patient. Instant claim 1 recites the use of a specific compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, in specific amounts, to treat complex regional pain syndrome. Thus, Rajkumar is missing the essential elements of the claimed invention using the specific compound in specific amounts.

Therefore, the teachings of Rajkumar cannot anticipate claim 1 because it fails to teach the claimed method for treating a specific disorder using a specific compound in a specific amount. Claims 6 and 8 are canceled, and thus the rejection is moot as to these claims. Because claim 9 depends from claim 1, it is not anticipated by Rajkumar. Applicant respectfully requests that the rejection by Rajkumar be withdrawn.

B. Claims 1, 6 and 15 are not anticipated by Olmarker, *et al.*

Claims 1, 6 and 15 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Olmarker, *et al.* (PCT publication WO 02080891). The Examiner alleges that claims 1, 6 and 15 are anticipated because Olmarker discloses a method of using thalidomide derivatives to treat low back pain. (Office Action, pages 14-15). Applicant respectfully disagrees.

Instant claim 1, as currently amended, recites a method of treating complex regional pain syndrome using specific amounts of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. Olmarker teaches use of a TNF-α inhibitor in treating nerve root injuries, without mentioning the use of the specific amount of the compound of claim 1, or the treatment of complex regional pain syndrome. Because Olmarker does not disclose methods of treating complex regional pain syndrome using the specific compound in a specific amount, instant claim 1 is not anticipated by Olmarker.

Claims 6 and 15 are canceled. Therefore, the rejection by Olmarker should be withdrawn.

IV. <u>Claims Rejections under 35 U.S.C. § 103</u>

A. Claims 2-5 and 23 are Patentable over Rajkumar, *et al.* in view of Merck.

Claims 2-5 and 23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Rajkumar, *et al.*, in view of the Merck Manual. (Office Action, page 15). Applicant respectfully disagrees.

Under the current law, prior art references cannot render a claim obvious unless the PTO provides evidence that the references meet a three-part test for *prima facie* obvious. To begin with, the prior art reference or references must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant." *See In re Kotzab*, 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000); *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 2005 WL 1355127, at *4, 75 U.S.P.Q.2d 1051, 1054 (Fed. Cir. 2005). Where one reference is relied upon by the PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See In re Kotzab*, 217 F.3d at 1370, 55 U.S.P.Q.2d at 1316-17. Where an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. *See WMS Gaming Inc. v. International Game Technology*, 184 F.3d 1339, 1355, 51 U.S.P.Q.2d 1385, 1397

(Fed. Cir. 1999); *Princeton Biochemicals, Inc.*, 2005 WL 1355127, at *4, 75 U.S.P.Q.2d at 1054; *Teleflex, Inc. v. Ficosa North America Corp.*, 299 F.3d 1313, 1334, 63 U.S.P.Q.2d 1374, 1387 (Fed. Cir. 2002).

Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *See In re Dow Chemical*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988); *Boehringer Ingelheim Vetmedica, Inc.*, 320 F.3d 1339, 1354, 65 U.S.P.Q.2d 1961, 1971 (Fed. Cir. 2003); *Noelle v. Lederman*, 355 F.3d 1343, 1352, 69 U.S.P.Q.2d 1508, 1516 (Fed. Cir. 2004). Further, "[b]oth the suggestion and the reasonable expectation of success 'must be founded in the prior art, not in the applicant's disclosure.'" *Noelle*, 355 F.3d at 1352, 69 U.S.P.Q.2d at 1515-16 (quoting *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991)). Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473, 43 U.S.P.Q.2d 1481, 1490 (Fed. Cir. 1997); *Litton Systems, Inc. v. Honeywell, Inc.*, 87 F.3d 1559, 1569, 39 U.S.P.Q.2d 1321, 1327 (Fed. Cir. 1996).

The Examiner alleges that claims 2-5 and 23 are obvious because Rajkumar teaches the use of thalidomide to treat complex regional pain syndrome, and Merck discloses that certain drugs, physical therapy and/or surgery can be used to treat regional pain syndrome. (Office Action, pages 15-16). Applicant respectfully disagrees.

The rejected claims are directed to methods of treating complex regional pain syndrome using a specific amount (about 5 to about 50 mg per day) of a specific compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, in combination with other agent or therapy. Rajkumar purportedly teaches the use of thalidomide alone to treat reflex sympathetic dystrophy. Rajkumar is silent as to 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, or its use. Rajkumar does not provide to one skilled in the art any suggestion or motivation to select any compound other than thalidomide, much less the specific compound in specific amounts as recited in instant claim 1, to treat complex regional pain syndrome. Furthermore, as the Examiner mentions (Office Action, page 15), Rajkumar discloses or suggests nothing about the use of a second therapeutic agent. Rajkumar does not even suggest any method of combination therapy as claimed. In sum, it has not been established that Rajkumar suggests the essential elements of the claimed invention herein, *e.g.*, the claimed methods

using 3-(4-amino-1 oxo-1,3-dihydro-isoindol-2-yl)-
piperidine-2,6-dione in specific amounts with second therapeutic agents for treating complex regional pain syndrome. That is, Rajkumar is missing any teaching or suggestion of essential elements of the claimed invention.

Merck does not cure the deficiency of Rajkumar. Merck discloses that certain drugs, physical therapy and/or surgery may be used to treat complex regional pain syndrome. However, Merck does not suggest the use of the specific compound in specific amounts for treating complex regional pain syndrome as recited in instant claim 1. Merck does not even suggest any method of combination therapy as claimed. Merck adds nothing to the disclosure of Rajkumar that would provide a suggestion or motivation to one skilled in the art to treat complex regional pain syndrome with the specific compound in a specific amount as recited in claim 1, in combination with a second therapeutic agent, treatment or surgery. Because the Examiner has provided no evidence of a teaching, suggestion or motivation for one skilled in the art to select the compound of claim 1 in a specific amount for the treatment of complex regional pain syndrome, with a second therapeutic agent, treatment or surgery, the instant claims cannot, and are not, rendered obvious by Rajkumar in view of Merck.

Next, the references cited by the Examiner do not suggest to one of ordinary skill in the art that the present invention would have a reasonable expectation of success. *See In re Dow Chemical*, 837 F.2d at 473. Neither Rajkumar nor Merck disclose the specific compound of the instant claims, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, much less specific amounts of the compound for use in complex regional pain syndrome. Rajkumar allegedly discloses the use of thalidomide. As is known to one skilled in the art, even slight modifications in structure can have substantial effects on the properties of a compound. Further, alleged obvious differences in specific chemical structures must be adequately supported in the prior art. *See* MPEP § 2144.09, citing *In re Grabiak*, 769 F.2d 729, 731-32, 226 U.S.P.Q. 871 (Fed. Cir. 1985). One skilled in the art would not be able to predict whether the recited compound in the present claims, alone or in combination, would be useful to treat complex regional pain syndrome in view of the teachings of Rajkumar. For these reasons, in view of Rajkumar and Merck, one skilled in the art would have no reasonable expectation that the specific compound of claim 1 in specific amounts and other agents in combination would be successful in the treatment of complex regional pain syndrome.

Finally, the Examiner has not met his burden of establishing that the prior art references, either alone or in combination, teach or suggest each and every limitation of the instant claims. *See Motorola, Inc.*, 121 F.3d at 1473. Again, Rajkumar and Merck do not disclose the specific compound of the instant claims, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, in specific amounts, much less its use in treating a specific disease. The use of thalidomide in Rajkumar together with the combination therapies of Merck is not enough to suggest the use of the specific amounts of the specific compound of claim 1, in combination with another therapeutic agent, to treat complex regional pain syndrome.

The Examiner, relying merely on conclusory remarks, has not provided factual, objective evidence to support his assertion that claims 2-5 and 23 are obvious in light of Rajkumar and Merck. *See In re Sang-Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002). Thus, the rejection must be withdrawn.

B. Claims 2-5 and 23 are Patentable over Olmarker, *et al.* in view of Merck.

Claims 2-5 and 23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Olmarker in view of Merck. The Examiner alleges that the instant claims are obvious because Olmarker discloses a method of using thalidomide derivatives to treat low back pain, and Merck discloses that certain drugs, physical therapy and/or surgery can be used to treat regional pain syndrome. (Office Action, page 17). Applicant respectfully disagrees.

Olmarker does not suggest using a specific compound--3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione--with additional agent or therapy, much less a specific amount of the specific compound, *i.e.*, about 5 to 50 mg/day of the recited compound. Moreover, Olmarker does not even suggest any methods of treating complex regional pain syndrome, much less the specifically claimed combination therapy. In sum, it has not been established that Olmarker suggests the essential elements of the claimed invention herein, *e.g.*, the claimed methods using 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione in specific amounts with other agent for treating complex regional pain syndrome. That is, Olmarker is missing any teaching or suggestion of essential elements of the claimed invention.

Merck does not cure the deficiency of Olmarker. Merck discloses that certain drugs, physical therapy and/or surgery can be used, without disclosing or suggesting the

use of the recited compound, much less the specific amounts, to treat complex regional pain syndrome.

Neither Olmarker nor Merck, alone or in combination, teaches or suggests a method for treating complex regional pain syndrome using a specific compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, much less a specific dose of the recited compound, in combination with another drug or therapy as claimed.

The Examiner has identified no teaching or suggestion that the recited compound in specific amounts may be used in treating pain, less complex regional pain syndrome, much less the combination therapy. Nowhere does Olmarker or Merck suggest or motivate the use of specific amounts of the recited compound with additional agent or therapy for treating pain, let alone complex regional pain syndrome. Thus, one of ordinary skill in the art would not have had a reasonable expectation of success from Olmarker and Merck. A *prima facie* case of obviousness has not been established and the rejection must be withdrawn.

C. The rejection of claim 16 under 35 U.S.C. § 103(a) is moot.

Claim 16 is rejected under 35 U.S.C. § 103(a) as unpatentable under Olmarker in view of Remington, *et al.*. (Office Action, page 18). Claim 16 is canceled, and thus, the rejection is moot.

V. Obviousness-Type Double Patenting Rejections

Claims 1, 6 and 15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over either claims 1 or 4 of U.S. Patent No. 5,635,517 ("the '517 patent"), or claims 1, 5, 9, 22 and 23 of U.S. Patent No. 5,955,476 ("the '476 patent"), in view of claims 1, 21 and 27 of U.S. Patent No. 6,635,250 ("the '250 patent"). Applicant respectfully disagrees.

The claims of the '517 patent and the '476 patent recite methods of reducing undesirable levels of TNF-α in a mammal using a species and genus of substituted 2,6-dioxopiperidine compounds. The instant claims are drawn to methods for treating complex regional pain syndrome using a specific amount of a specific compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. The cited patents do not disclose or suggest the methods of treating complex regional pain syndrome using the specific amounts of the recited compound as in the instant claims of the instant application. The Examiner himself admitted that the cited patents do not disclose

methods of treating neuropathic pain. (Office Action, page 20). Thus, the subject matters of the patents and the present application are not encompassed by each other.

The claims of the '250 patent relate to methods of treating a nerve disorder mediated by nucleus pulposus or caused by a herniated disc using a specific TNF-α inhibitor, metalloproteinase inhibitor. The pending claims, as amended, recite methods of treating complex regional pain syndrome using a specific amount of a specific compound, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. The '250 patent does not disclose or suggest the specific compound as recited in the instant claims to treat complex regional pain syndrome. Thus, the subject matters of the '250 patent and the present application are not encompassed by each other.

Accordingly, the pending claims are patentably distinct from the claims of any of the cited patents, and the rejection must be withdrawn.

The Examiner also rejected claims 1 and 6 as unpatentable over any of 12 issued U.S. patents (US Patent Nos. 5,635,517; 5,955,476; 5,798,368; 5,698,579; 5,736,570; 5,703,098; 6,395,754; 6,180,644; 6,130,226; 6,075,041; 6,214,857; 5,968,945) in view of the '250 patent (Office Action, page 21). Applicant respectfully disagrees.

The 12 patents cited by the Examiner are drawn to methods of reducing undesirable levels of TNF-α in a mammal using a TNF-α inhibitor including a species and genus of substituted 2,6-dioxopiperidine compounds. Claims 1, 21 and 27 of the '250 patent recite methods of treating a nerve disorder mediated by nucleus pulposus or caused by a herniated disc using a specific TNF-α inhibitor, metalloproteinase inhibitor.

The Examiner himself admitted that none of the 12 patents cited in combination with the '250 patent disclose or suggest a method of treating neuropathic pain, not to mention the specific disorder of complex regional pain syndrome. (Office Action, page 21). The cited patents do not disclose or suggest methods of treating complex regional pain syndrome using a specific amount of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, as claimed in the present application. Therefore, the pending claims in the present application are patentably distinct from the claims of the cited patents.

In sum, Applicant respectfully submits that the rejection of the pending claims under the judicially created obviousness-type double patenting should be withdrawn because no *prima facie* case of obviousness has been established for the pending claims

over any of the cited patents. Applicant further submits that no terminal disclaimer over the cited patents is necessary.

Conclusion

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above amendment and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Please apply fees for the Extension of time ($450) and any other charges, or any credits, to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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